Remarks / Arguments

Claims 10, 13 and 14 are pending in this application. Claims 10, 13 and 14 have been amended. Claims 11-12 and 15-16 have been cancelled.

Rejection under §103

Claims 10-12 and 15-16 stand rejected under §103 as being unpatentable over Haning (WO 98/40384, US 6,174,884) in view of Merck Manual, Home edition 1997, pages 12-15, 381-387, 398-402.

Claims 11-12 and 15-16 have been cancelled. The rejection of these claims is thus moot, and its withdrawal is accordingly requested. These cancellations leave only claim 10 being rejected.

In particular, 10-12 and 15-16 have been rejected on grounds that the Haning reference teaches a method of treating cerebrovascular diseases (e.g., stroke) comprising administering to a patient a PDE-II inhibitory compound of formula (I), such as the compound represented by example 39 Haning, while the Merck reference teaches visual changes, dementia and depression can result from stroke.

For the reasons given in applicants' response dated 8 March, 2004, Applicants believe Examiner's rejection is improper. Haning discloses compounds which are stated to be useful for treatment of cardiovascular and cerebrovascular diseases, and states that these compounds inhibit either one of more of the c-GMP-metabolizing phosphodiesterases PDE I, PDE II and PDE V, leading to an increase in c-GMP. The reference states that the compounds can be used in medicaments for treating cardiovascular diseases, and provides a large list of exemplary

cardiovascular diseases (including stroke). It also states that the compounds can be of importance for cerebral vascular diseases.

The Haning reference does not state that all the compounds it discloses are PDE II inhibitors. Rather, it states that the compounds inhibit one or more of PDE I, PDE II, and PDE V. Five compounds were tested for phosphodiesterase inhibition in vitro against PDE I, PDE II, and PDE V. Each of the tested compounds was shown to inhibit PDE II with an IC_{50} of between 100 and 500 nM. No test data were presented for other exemplary compounds. Thus, the reference only discloses that 5 tested compounds are PDE II inhibitors. The reference is silent with respect to the PDE II inhibitory activity of the remaining exemplary compounds.

Haning does not disclose that any of his compounds are selective PDE 2 inhibitors as the term is defined in the present claims. Furthermore, although seven exemplary compounds of Haning (examples 18, 36, 39, 40, 49, 50, and 85) fall within the structural formula of present claim 10, none of these was tested by Haning and shown to be a PDE II inhibitor.

The Haning reference does state that the compounds there disclosed and claimed can be used in medicamcnts for treating a long list of cardiovascular diseases, one of which is stroke. However, there is no suggestion that stroke should be selected from the list of conditions to be treated (as opposed to any of the other diseases listed), and no suggestion that the subset of compounds identified in the present invention (as opposed to any of the other compounds of the reference) should be employed for treatment of stroke.

The examiner argues that the Merck reference teaches that visual changes, dementia, and depression can result from stroke (page 382, col. 2, page 384, col. 1, and page 399, col. 1). Page 382 describes the symptoms of transient ischemic attacks. Page 383 describes the possible symptoms of stroke as depression or inability to control emotions, as well as the symptoms described for transient ischemic attacks, none of which relates to the improvement of learning, as is now claimed. Page 385 describes neurologic loss. Page 399 describes dementia, and defines it as, among other conditions, an impaired ability to learn.

There is no motivation in Haning or Merck to combine their respective teachings and to arrive at the presently claimed invention. In addition, the examiner does not explain why there would be any reasonable expectation of success resulting from such combination, but simply states that from the above one of ordinary skill in the art would expect to employ Haning's compounds to treat stroke and thereby treat loss of memory and disorders of perception. The examiner does not explain why one of ordinary skill in the art would select from Haning's broad disclosure of compounds with activity against PDE I, PDE II, and PDE V just the very subset of selective PDE II inhibitory compounds of the present invention. This constitutes hindsight reconstruction, and is improper.

However, in order to expedite prosecution, Applicants have amended claim 10 to be directed to a method for improving learning or memory. Applicants believe the limitations of present claim 10 are not taught by the cited references and that the amendment overcomes the Examiner's rejections.

Applicants furthermore direct the examiner's attention to Fig. 2 and the object recognition test as described on page 11 of the text as filed, wherein the changes in discrimination index of rats after treatment according to the present invention are described. Here the memory capacity of the animal group treated with 0.3 mg/kg or 1.0 mg/kg of Example 1 exhibited an elevated discrimination index. As described on page 11, lines 10 and 28 *et seq.*, such discrimination index expresses memory ability of the rats.

The compounds of the invention thus have been shown to have unexpected pharmacological properties. For this reason, they were not obvious at the time the invention was made. Accordingly, reconsideration and withdrawal of the rejection of claim 10 is requested.

The examiner has indicated that claims 13 and 14 would be allowable if rewritten in independent form including all of the limitations of the base claim. Claims 13 and 14 have been rewritten in such form.

In view of the above amendments and arguments, this application is deemed to be in condition for allowance, and allowance is accordingly requested. Please charge any further fees due with this amendment to deposit account number 13-3372.

Respectfully submitted,

William F. Gray

Reg. No.: 31018
Phone: (203) 812-2712
Date: 28 December 04

William F. Gray
Bayer Pharmaceuticals Corporation
400 Morgan Lane
West Haven, CT 06516-4175